REMARKS

Consideration of the above-identified patent application, as amended, is respectfully requested. Claims 128-131 have been rejected on various grounds, but these claims have now been cancelled and the rejections are therefore moot. New claims 132-174 have been added and it is submitted that these claims are patentable over the art for reasons set forth hereafter.

Claims 132-174

The newly submitted claims are distinguishable over the prior art on several grounds. A common thread running through the prior art was the belief and expectation that pharmaceutical formulations of FSH would not be stable for a prolonged period of time sufficient to allow multiple administrations to a patient. The art taught the instability of such formulations, and the real world followed by commercially selling FSH for thirty years with indications that the FSH formulations should be used upon reconstitution, and not over a period of time. However, the present invention – providing stable and preserved FSH formulations useable over a period of time - is now embodied in commercial products which are being touted for the ease, convenience and reliability of use over extended treatment regimens.

The claims currently in the application reflect the stable and preserved formulations which eluded the art for those 30+ years. Claim 132, for example, provides a method for administering FSH using a relatively low concentration of FSH in a formulation containing benzyl alcohol. The formulation is packaged in a vial, and the method involves administering first and second pharmaceutically-effective amounts of FSH to a patient over a period of greater than 24 hours. The prior art has failed to teach or suggest an FSH formulation that was administered to a patient over multiple days. Claims 135-137 address administering the FSH formulation over even longer periods of time. Claim 139 provides a comparable method of administering FSH over a period of time, but does not specify that the formulation is provided in a vial – e.g., it could be prepared by the patient as a reconstituted formulation. Similarly, claim 143 provides a method which relies upon the stable and preserved FSH composition by holding the

composition for 24 hours before use. Claim 147 proscribes a related method in which two portions of the composition are administered at least 24 hours apart. Again, the prior art failed to teach or suggest a method which involved administering an FSH formulation over an extended period of time, as addressed by the foregoing claims.

Claims 152 and 158 relate to the preparation of a stable and preserved FSH formulation. The prior art did not teach or suggest FSH formulations that would have been known or expected to be stable for extended periods of time, and therefore the prior art formulations of FSH reconstituted by a patient or health care provider were used immediately. For more than thirty years of commercial sales, there was no indication that the FSH formulations would be used over an extended period of time. In contrast, claim 152 provides a method for preparing a stable and preserved FSH formulation not disclosed or made obvious by the prior art. Claim 153 relates to storing the vial of FSH formulation for more than 2 months – something which would not have been contemplated by the prior art. Claim 154 is directed to providing multiple doses in the vial, thereby providing a patient with an amount that permits administration of the FSH formulation over a period of time. Claims 155 and 156 even more explicitly indicate that the amount of FSH formulation in the vial is sufficient for administration over a period of days. Claim 158 also relates to the preparation of a stable and preserved FSH formulation, comprising reconstitution of a lyophilized mixture of FSH and a lyoprotectant.

Claims 159 et seq. are directed to the FSH formulations themselves. As suggested by the Examiner, these claims incorporate limitations related to the stability of the formulations, and are distinguishable from the prior art on that basis (as well as other bases). Claim 159, for example, relates to an FSH composition in which a relatively low concentration of FSH is present in the solubilized, biologically-active, heterodimeric protein form, with the alpha-subunit and beta-subunit held together by noncovalent interactions. The FSH referenced in the claim therefore is not significantly present in the dissociated form. Certain of the related dependent claims are directed to properties of the FSH, such as the fact that greater than 99% of the FSH particles have an indicated average diameter (claim 162) or are provided by the heterodimeric form (claim 163). Such limitations further address the fact that the FSH is present in a stable, biologically-

active form. Claim 168 covers an FSH composition in which the stability of the FSH is indicated by the fact that an effective dose of biologically active FSH is provided even after the composition has been held for 24 hours.

Claims 134, 169 and 170 are directed specifically to the use of recombinant FSH or substantially pure FSH. It has been noted in the prior art that problems with dissociation are more prevalent for recombinant or other highly purified forms of FSH. The lack of expectation of stability for formulations of these forms of FSH has been even more evident as a result. In contrast, the present invention provides stable and preserved formulations of recombinant FSH and/or substantially pure FSH.

Reconsideration of the above-identified application, as amended, is therefore respectfully submitted. As demonstrated in previous submissions, including affidavits of persons knowledgeable of the art, the present invention is clearly and patentably contrasted from the prior art. There had been a long felt and resolved need for improved administration of FSH formulations, and this invention has provided the easy, convenient, and long term administration that is touted in the commercial arena after 30 years of inferior approaches. In the quest for improved administration of FSH formulations, the availability of such stable and preserved formulations was unexpected, and has rapidly become the adopted approach in the industry.

Respectfully submitted,

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